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REVIEW ARTICLE

Microbeam radiation therapy — grid therapy and beyond: a clinical perspective

[1]ELISABETH SCHÜLTKE, MD, PhD, [2]JACQUES BALOSSO, MD, PhD, [3,4]THOMAS BRESLIN, MD, PhD, [5]GUIDO CAVALETTI, MD, PhD, [6]VALENTIN DJONOV, MD, [2]FRANCOIS ESTEVE, MD, PhD, [7]MICHAEL GROTZER, MD, [1]GUIDO HILDEBRANDT, MD, PhD, [8]ALEXANDER VALDMAN, MD, PhD and [6]JEAN LAISSUE, MD

[1]Department of Radiooncology, Rostock University Medical Center, Rostock, Germany
[2]Departement of Radiation Oncology and Medical Physics, University Grenoble Alpes (UGA) and Centre Hospitalier Universitaire Grenoble Alpes (CHUGA), Grenoble, France
[3]Department of Oncology, Clinical Sciences, Lund University, Lund, Sweden
[4]Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden
[5]Experimental Neurology Unit and Milan Center for Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy
[6]Institute of Anatomy, University of Bern, Bern, Switzerland
[7]Department of Oncology, University Children's Hospital of Zurich, Zurich, Switzerland
[8]Department of Oncology and Pathology, Karolinska University Hospital, Stockholm, Sweden

Address correspondence to: Dr Elisabeth Schültke
E-mail: *elisabeth.schueltke@med.uni-rostock.de*

ABSTRACT

Microbeam irradiation is spatially fractionated radiation on a micrometer scale. Microbeam irradiation with therapeutic intent has become known as microbeam radiation therapy (MRT). The basic concept of MRT was developed in the 1980s, but it has not yet been tested in any human clinical trial, even though there is now a large number of animal studies demonstrating its marked therapeutic potential with an exceptional normal tissue sparing effect. Furthermore, MRT is conceptually similar to macroscopic grid based radiation therapy which has been used in clinical practice for decades. In this review, the potential clinical applications of MRT are analysed for both malignant and non-malignant diseases.

GRID-BASED RADIATION THERAPY

Grid-based radiation therapy is spatially fractionated radiotherapy. It was developed and first reported by the German radiologist Alban Köhler in 1909, to reduce the extensive damage of skin and subcutaneous tissue occurring following the irradiation of deep-seated tumours.[1] Although Köhler's grid therapy was disparaged until the 1930s, it has since been used successfully in clinical radiotherapy to shrink large malignancies.[2–5]

With the advent of megavoltage radiotherapy and the introduction of linear accelerators (Linac) into clinical radiotherapy in the 1970s, modern radiotherapy was confronted with new challenges: while adverse skin reactions were no longer a limiting factor, dose limitation is now seen in the normal tissues tolerance of other organs such as lung, brain and intestine. Also, patients with bulky tumours who, at earlier times, would have been deemed incurable and referred to palliative therapy, have now become eligible candidates for radiotherapy.

Mohiuddin et al[6] developed a grid therapy concept that could be used with megavoltage radiotherapy, naming it appropriately GRID. They used a specially designed Cerrobend® grid matrix which can be fitted into the tray holder of commercially available Linacs. The matrix had 256 holes of 7.5 mm diameter in a 16 × 16 cm matrix; the ratio of open to blocked areas was 50:50. The maximum treatable area at the isocentre was 20 × 20 cm. The high dose heterogeneity created by the Cerrobend® grid matrix is even maintained at larger depths in tissue. Thus, the recovery processes characteristic of grid therapy will even occur in the low dose regions well below skin level.[7] Based on the results from 71 patients with advanced bulky tumours (≥8 cm diameter), where GRID was administered either as single fraction of up to 20 Gy or included in a conventionally fractionated radiotherapy schedule, better tumour control was achieved than with conventional treatment alone.[8]

In 2006, Ha et al[9] published the results of a feasibility study using a multileaf collimator (MLC) to shape a grid-like

irradiation field. Since the MLC function was already part of the clinical treatment planning system, the integration of a grid-like MLC function into conventional radiotherapy schedules was much easier. The open-to-closed field ratio using the MLC was lower than with the Cerrobend® grid matrix and the treatment time longer. Nevertheless, if the treatment results were comparable, no additional construction would be needed in future for megavoltage grid therapy.

In an attempt to further develop the concept of grid therapy, a research group from Stockholm has recently published a proof-of-concept study investigating the possibility of merging the grid treatment approach with proton therapy.[10]

To date, several clinical trials on grid radiotherapy are listed at the website of the U.S. National Institutes of Health. Target groups include patients with bulky and/or radioresistant tumours, particularly squamous cell carcinomas of the head and neck, and paediatric osteosarcomas of the extremities ().

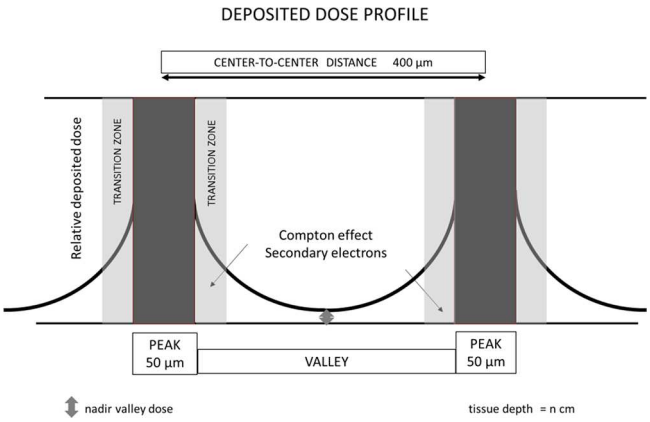
MRT: grid therapy at the micrometer scale?

Curtis, Zeman and coworkers reported in the 1960s the first surprising results with spatial fractionation of ionizing radiation in the microscopic range following a series of studies on the effects of cosmic radiation. While deuteron irradiation at a dose of about 140 Gy delivered in a 1 mm wide beam resulted in blood vessel damage and tissue necrosis, the same dose delivered in a 25 μm (*i.e.* 0.025 mm) wide beam caused no damage within a 240 days observation period. Only at and above doses of 4000 Gy, nerve and glial cells in the path of a 25 μm wide beam died within 24 days after irradiation. However, there was no permanent damage to blood vessels and the overall tissue architecture remained intact. In sharp contrast, exposure to a 1-mm wide beam caused complete tissue destruction and subsequent cavity formation.[11]

When the NSLS (Brookhaven, Upton, NY) became available as a new synchrotron source, Slatkin and his colleagues, driven by personal knowledge of the extraordinary results obtained by Curtis and his group, decided to investigate the effects of planar, synchrotron-generated X-ray microbeams on mouse brains. The tissue lesions seen after those experiments resembled the lesions induced by deuteron microbeams.[11] Surprisingly, no tissue necrosis developed in the brains of animals after focal administration of hundreds, even thousands of gray delivered along the peak dose zones of microbeam arrays.[12] The dose heterogeneity determined by the collimator inserted into the primary synchrotron X-ray beam was maintained at large tissue depths and the repair processes characteristic for spatially fractionated fields occurred well below skin level, in contrast to the divergence and obliteration of the grid pattern of the first grid therapies. As Börje Larsson[13] had proposed to use synchrotron X-rays for radiosurgical applications, the radiotherapeutic potential of microbeam arrays was explored by irradiating orthotopic intracerebral 9L gliosarcomas in rats.[14]

Microbeam irradiation with therapeutic intent hails both from grid therapy and the miniaturization of X-ray beams and has

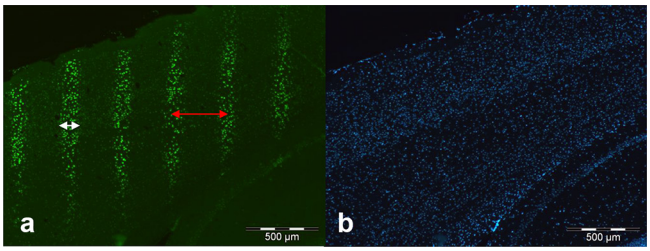
Figure 1. The primary X-ray beam is split by insertion of a collimator into an array of quasi-parallel microbeams. As a result, peak-dose, valley-dose and transitional zones are generated in the tissue (modified after).[15]



become known as microbeam radiation therapy (MRT). It is characterized by a spatially and periodically alternating microscopic dose distribution. Contrary to most concepts used in clinical radiotherapy, dose deposition in MRT follows an inhomogeneous geometric pattern with so-called peak dose zones and valley dose zones (Figures 1 and 2). An array of quasi parallel microbeams is generated by insertion of a specially designed collimator into the primary X-ray beam characterized by a high photon flux. One of the main reasons for the "miniaturization" of MRT compared to the original grid therapy is geometrical: "miniaturization" has increased the contact surface between swaths of heavily and lightly irradiated tissue, where wound healing occurs, by more than an order of magnitude, enabling the instantaneous, short distance access of lightly irradiated cells and humoral mediators to the damaged peak regions.

The high photon flux of a synchrotron X-ray beam is required in order to generate arrays of quasi-parallel microbeams at a dose rate of 100 Gy s^{-1} or higher to assure overall irradiation times of seconds or fractions of seconds. A very short irradiation time is a prerequisite to obtain a precise MRT dose distribution in living tissue since any movement of the target tissue in the micrometer

Figure 2. (a) Immunostain (H2AX) of adult mouse cerebral cortex, illustrating the characteristic pattern of DNA double strand breaks (bright green dots) caused by irradiation with an array of quasi-parallel microbeams (≈50 μm wide, white arrow), spaced ≈400 μm from centre to centre (red arrow), two hours after exposure (C. Fernandez-Palomo and E. Schültke, unpublished). (b) DAPI stain to demonstrate the presence of nuclei (blue dots) in the same section as in a.



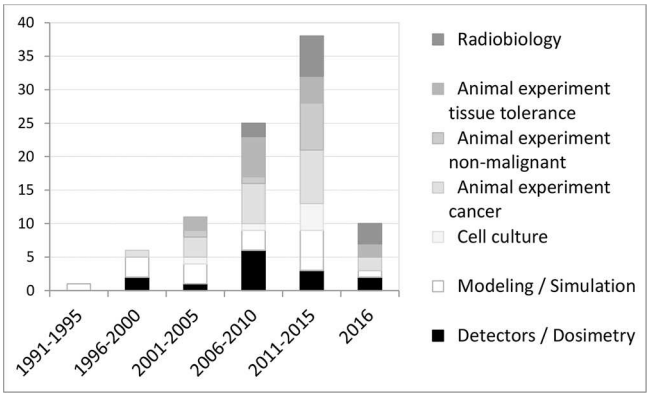
or even millimeter range, which is the norm rather than the exception, will obviously disrupt the required dose distribution. With the broad beam irradiation concepts currently used in conventional radiotherapy, tissue movements in this range are of little consequence. In MRT, with beams at the micrometer scale, longer irradiation times would result in dose smearing at the edge of each microbeam, preventing the sharp dose fall-off between microbeams and the normal tissue sparing resulting from this dose distribution would be completely lost.

It is very difficult to define tolerance doses to compare homogeneous field radiotherapy with macroscopic and microscopic grid therapy. The linear-quadratic (LQ) model and the concept of biologically effective dose (BED) were developed for spatially homogeneous radiation, to compare biological effects occurring with temporal fractionation and the variation of dose per fraction. In radiosurgery it is said that the tumour control observed clinically is often underestimated by the LQ model. No consideration has yet been taken of the effects caused by the variations in treatment time associated with many forms of radiosurgery, or of the very significant dose variation within the target associated with many approaches to radiosurgery. Consequently it has been proposed that current approaches do not reflect vascular and stromal radiation damage and neglect the impact of radioresistant subpopulations of cells.[16] However, alternative approaches remain unproven. Due to the dose distribution (dose-volume effect), typical peak doses in microbeam irradiation are usually higher, compared to the macroscopic GRID techniques in clinical radiosurgery, by more than one order of magnitude. Thus some factors associated with the LQ model, namely clonogenic cell survival, might not have the same importance because acute cell death rather than a loss of cell clonogenic potential could be the overriding mechanism of damage.

In the last decade, many studies have been directed towards obtaining a better understanding of the biological basis of the differential effects of microbeam irradiation on tumours and normal tissues. Several studies support the hypothesis that microbeam irradiation exerts different effects on the vasculature of tumours and of normal tissues.[16–26] The importance of the stromal radiation response was highlighted by the results of studies showing that normal tissue and tumour tissue differ in their response to MRT. A proteomic study in rodent brain has shown that microbeam irradiation-induced bystander effects were potentially antitumourigenic and based on ROS-induced apoptosis, where broad beam irradiation with comparable integrated doses induced proteomic changes that have previously been associated with tumorigenesis or cancer development.[27] Also, there is evidence for the differential regulation of genetic pathways involved in MRT and broad beam irradiation.[28,29] Surprisingly, even the genetic profile of cells and tissues seems to change after MRT.[30–33]

A series of studies reporting bystander and abscopal effects was published after collaborative work between the group of Elisabeth Schültke and the radiobiology laboratory of Carmel Mothersill.[34–38] Bystander effects were also reported by another research group.[39]

Figure 3. Distribution of publications in the field of MRT according to field of specialization, also illustrating the trend from exclusively cancer-oriented work to the inclusion of non-malignant diseases as therapy targets. Abscissa: number of publications.



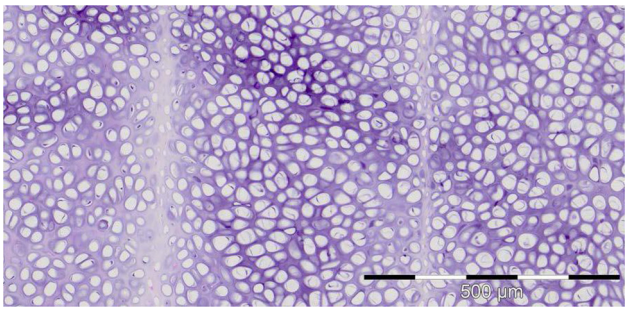
Beginning in the 1990s, there has been a steady increase in the number of publications per year reporting on the advancing technical development and the biological effects of MRT.

During the first decade of the development of MRT, publications described the development of hardware components, since commercially available therapy planning systems were not suited for work with X-ray beams at the micrometer scale. Also, potential patient target group selection was discussed, starting with the publication by Slatkin in 1992.[40] New detector systems were developed[41] and Monte Carlo calculation was used in mathematical modeling to understand the challenging basics of MRT dosimetry.[42]

In the early days of MRT development, the therapeutic targets were exclusively thought of as being in the field of oncology. In 1998, Laissue et al[14] were the first to report on the therapeutic efficacy of MRT in a small animal model of malignant brain tumour. Four years later, the first paper on the potential suitability of MRT to treat non-malignant vascular disease was published.[43] Soon after therapeutic efficacy of MRT had been established in small animal models, normal tissue tolerance to MRT moved into the focus of interest. The first paper addressing this subject was by Laissue et al,[44] reporting on therapeutic efficacy and high normal tissue tolerance, the latter specifically in normal young suckling rats. Thus, three clinically important themes were defined: MRT as treatment approach in oncology, in the treatment of non-malignant diseases and the need to define normal tissue tolerance (Figure 3).

While more and more biological data were being collected to support the transfer of MRT from the laboratory into a clinical trial, work on hardware and software components to fit the safety criteria of a clinical trial was intensified, including the development of the image-guidance system.[45–51] New detector systems were developed to satisfy the specific requirements of microdosimetry.[52–54] New simulation approaches included mathematical modeling and the testing and adaptation of medical physics models into the synchrotron environment.[55–58]

Figure 4. Rabbit, maxilla, 411 days post irradiation. H&E stain of cartilage traversed by a quasi-parallel array of microbeams; valley dose ≈10 Gy; the general tissue structure appears unchanged (Laissue et al unpublished).



In order to intensify efficacy at the target, the likely influence of new irradiation geometries was tested, including beam arrays generated by two or more ports crossing at the target location in different planes.[59] The generation of pencil beams was tested successfully in the hope that this might result in even higher normal tissue tolerance doses.[60] Dose enhancement was looked at in relation to MRT, especially with nanoparticles.[61,62] Advice was produced for the optimal energy spectrum to be used in any clinical trials of MRT.[26,63]

Oncological targets: MRT as boost after conventional RT

The prognosis of some patient groups with highly aggressive and radioresistant tumours is still very poor. Work in animal models of malignant disease has shown that the development of highly aggressive tumours can be delayed or even ablated by MRT.[14] In most clinical radiotherapy schedules, single fraction doses are between 1.5 Gy and 3 Gy. The typical peak doses in MRT are several hundred Gy. It is assumed that such high doses can be tolerated by normal tissue due to the relatively small volume of tissue directly in the path of microbeams (Figure 4).

Three oncological targets which could profit from MRT are discussed: malignant brain tumours, lung cancer and malignant tumours of the musculoskeletal system.

Although brain tumours account for only 1% of the annual incidence of malignant tumours, they account for as much as 25% of all cancer deaths.[64] Meta-analyses have shown that radiotherapy is the only one independent predictive prognostic factor in treatment.[65] However, little gain in survival time can be obtained for many patients with malignant brain tumours. For patients with high grade gliomas like anaplastic astrocytoma or glioblastoma multiforme, the average survival time from diagnosis is between 1.5 and 3 years.[66,67] However, in long-term survivors, significant cognitive deficits have been reported.[68] Thus, primary tumours of the central nervous system were the first focus for pre-clinical MRT research. Increased survival times were reported as well as little to no decrease of cognitive function in long-term survivors after MRT.[69]

Because the rat spinal cord has a high tolerance to exposure to parallel microbeams,[70] MRT might also prove useful in the treatment of malignant lesions in or near the spinal canal of children and/or adults.

Pre-clinical MRT studies have been designed to replace an entire conventional radiotherapy schedule with one single treatment session of MRT, similar to the approach already established for clinical radiosurgery. However, an equally or even more effective approach might be the integration of MRT as boost into a conventional radiotherapy schedule, where the valley dose used could match the daily fraction of the conventional therapy schedule, and the peak dose act as boost.[71] The aim of such an approach would be to improve tumour control as well as to shorten the overall treatment time.

Advanced lung cancer is the number one cause of cancer death in adults in Europe and North America. About 25% of all tumour patients are those with lung cancer and with an incidence of 60 in 100,000 in the population, they belong by far to the largest patient group currently with unsatisfactory treatment concepts.[72] The overall outcome is poor and average survival time after diagnosis is 2.5 years, as stated in a review by the U.S. National Institutes of Health.[73] Surgical removal of the tumour is often not possible and resistance to chemotherapeutic agents frequently develops within the first year after the commencement of chemotherapy. Thus, radiotherapy is then the only therapeutic option left to extend the life of these patients. However, conventional radiotherapy of the lung carries a high risk of the development of pneumonitis, an inflammatory condition of the lung caused by irradiation that frequently results in lung fibrosis, either resulting in death or severely reduced quality of life.[74] Because of individual institutional approaches regarding contouring and target definition on the one hand and the observational skills of the treating physician on the other hand, the reported incidence of radiation-induced pneumonitis varies widely. Keeping in mind that the risk of radiation-induced pneumonitis also increases with the irradiated volume, a recommendation is that the mean lung dose be limited to less than 20–23 Gy outside the treated area[75]; in fact, less than 13 Gy are applied in several centres.The fairly recent concept of stereotactic body radiotherapy, applicable to one or two lesions, it is not feasible for large volumes. Thus, a new radiotherapy concept characterized by both the application of a very high single fraction dose and a high normal tissue tolerance would be highly desirable. The pre-clinical experience with brain tissue has inspired the hope that similarly minimal morphological damage and functional deficits will be seen after MRT in lung tissue.

The multiple alveolar interfaces between air and tissue make the dose calculation for MRT very challenging.[76,77] An initial *in vivo* experiment has been conducted but the results have not yet been published (personal communication).

Patients with malignant tumours of the musculoskeletal apparatus like sarcomas or chondrosarcomas also belong to one of the patient groups currently without satisfactory treatment approaches.[78,79] For these patients, the 'best' solution, *i.e.* the solution offering the longest progression-free interval, is the amputation of the affected extremity.[80] The final prognosis

in his disease is most likely determined by the development of metastatic disease. However, if the primary tumour can be controlled, this might also delay the development of metastatic disease. Removing the present necessity for amputation would be an extremely significant improvement in the quality of life of afflicted patients.

The potential of MRT in the treatment of epilepsy

An increase in the interest in the potential of MRT for the treatment of non-malignant diseases was noted in the last few years. Epilepsy is the most widely explored field to date. Temporal lobe epilepsy, the most common form of pharmaco-refractive epilepsy, is associated with and probably caused by hippocampal sclerosis in about 65% of the patients.[81] The standard treatment is surgical amygdalo-hippocampectomy.[82,83] The hippocampus is the morphological equivalent of new memory formation for which at least one hippocampal formation needs to be present and functionally intact. Thus, in patients with multiple bilateral epileptogenic foci in the hippocampal formation, a seizure-free status often cannot be achieved surgically.

The concept to use MRT in a similar way to the already clinically established approach of radiosurgery but with a much higher precision to treat otherwise therapy-resistant epilepsy was proposed by the research group of Romanelli.[84,85] Pouyatos et al[86] published the results of an experimental proof of concept study about interlaced MRT. This involved a new microbeam irradiation geometry that delivers a homogeneous dose to mm^3-sized epileptogenic foci of rat brain and thus abolishes or reduces the measured epileptogenic potential. Romanelli et al[87] described seizure control in a small animal model by transection of the sensorimotor cortex by microbeams without significant neurological deficit. The initial work on interlaced MRT was followed up later, correlating the reduction of seizures after applying MRT with electrophysiological and histological data.[88] A third paper contributed by this group reported successful therapeutically efficient image-guided interlaced microtransections in mm^3-sized eloquent cortical areas in a small animal model of generalized epilepsy.[89]

Carbon nanotube X-ray and proton microbeams

While this review focuses mainly on microbeams generated on the base of X-rays, the last decade has also seen successful efforts to generate microbeams based on sources such as protons and carbon nanotube X-rays.

While X-ray-based microbeam studies have almost exclusively been conducted with arrays of quasi-parallel microbeams, proton microbeam studies have been conducted both with single microbeams and microbeam arrays. For proton microbeam arrays, a thorough study of the interdependence of beam energy, the centre-to-centre distance of the microbeams and the target depth was published by Klodowska et al.[90] In a comparative study, increased normal tissue tolerance for both acute and long-term damage, compared to broad beam irradiation, was shown for both X-ray-based and proton-generated microbeam arrays.[91]For single proton microbeams, Buonanno published the results of a study showing therapeutic efficiency in a small animal model of melanoma[92] and chromosomal rearrangement was described as a consequence of proton microbeam irradiation.[93]

The nanotube-based electron microbeam irradiator was introduced in 2008.[94] This was followed by Monte Carlo calculations for a compact nanotube microbeam system.[95] The first biological paper showing the effects of such beamlets was for brain tissue.[96] Compared to centre–to-centre distances (ctc) typical for X-ray-based microbeams (≤100 μm), the separation distances in this experiment were 1.4 mm. One year later, a paper was published exploring the results of theoretical work with beamlets as narrow as 290 μm,[97] followed by a study that proved therapeutic efficacy of the method.[98] The latter worked with a beamlet width of 280 μm and a centre-to-centre of 900 μm. Thus, the irradiation geometry is more comparable to the wider X-ray-based minibeams than to the microbeams which are the focus of this review. For X-ray-based beam arrays it has been shown that, given the same peak dose, normal tissue tolerance decreases with increasing beam width.[99] Even more interestingly, the differential effect between mature and immature tissue, on which part of the typical action of MRT is based, was not observed for minibeams. The results published by Uyama support the idea that tumour control is improved by the use of narrow microbeams.[100]

DISCUSSION

Grid-based radiotherapy concepts have been developed and clinically used at several stages in the history of radiotherapy to push the limits of what radiotherapy can achieve for cancer patients. MRT as grid-type therapy but at the microscopic level offers a new route to dose escalation without compromising surrounding normal tissues. Just like the first grid therapy invented by Köhler[1] at the beginning of the 20th century, MRT allows the increase of dose in regularly spaced areas of the irradiation field and protects normal tissue morphology and function.

Grid therapy at the macroscopic level, with a beam width in the millimeter range, has been used successfully in the clinical radiotherapy environment. The high dose heterogeneity created by the Cerrobend® grid matrix is maintained even at larger tissue depths.

Microbeam radiotherapy, on the other hand, is still an experimental concept at the pre-clinical stage. The sharp dose fall off is even more pronounced with the kilovoltage radiotherapy, as compared to the macroscopic grids used in megavoltage radiotherapy by Mohiuddin's group. Due to a lower dose scattering effect in this energy range, MRT dose simulations show a sharper in depth dose fall off.[23]

The results contributed by a number of research groups over the last decades suggest that tissue responses to broad beam and microbeams are dramatically different with regard to both genetic and physiologic factors. We expect that the efficacy of MRT, quite likely integrated in a conventional therapy schedule, will by far surpass that seen in macroscopic grid therapy.

The antineoplastic efficacy of MRT for tumour volumes around 10 to 15 $cm^{3,}$ at tissue depths of several centimeters is presently being tested tested pre-clinically.

The most important aspects of any clinical trial for the treatment of cancer in patients are feasibility and safety. It is expected that with MRT survival time can be increased and the quality of life can be improved substantially for the remaining life span by improving local tumour control. The latter might be done by the shortening of overall treatment times or / and the preservation of limbs affected by cancer.

One of the most common risk factors for developing a cancer is increasing age. Considering the steadily increasing life expectancy in all industrialized nations, within the coming decades it can be expected to see a significant increase in the number of elderly patients developing one or more cancers late in their lives. More than ever, increasing the quality of life for these patients will be equally if not more important than a mere extension of life span.

For glioblastoma multiforme, a highly malignant brain tumour with a strong age peak in the patient group above 60 years of age, the average survival time is less than two years after diagnosis. In the younger age group, diffuse infiltrating glioma affects most frequently children in the first decade of their lives. While there is only limited survival time to be gained with any therapeutic approach, radiotherapy can result in a significant temporary improvement of neurological symptoms. For very young children, radiotherapy requires a general anaesthesia. A radiotherapy schedule running over six weeks with five weekly fractions means a heavy logistic as well as emotional burden on the patient, the family and the medical staff. Paediatric patients with diffuse intrinsic pontine glioma (DIPG), for instance, might be an excellent target group for MRT.[101]

A shortened hospital stay and the opportunity to be at home can be an important contribution to a better quality of life, regardless of the age. MRT used as single fraction or as integrated boost in combination with a conventional radiotherapy schedule, where the MRT valley dose is equal to a single fraction dose of the conventional radiotherapy schedule, could shorten the overall treatment time significantly.

Where longer survival times can be achieved by using improved treatment schedules, radiogenic encephalopathy with its cognitive defects becomes an issue. It is known that the clinical symptoms of encephalopathy increase with increasing irradiated volume.[102] Experimental data have shown that MRT causes relatively few functional deficits.[69,103]

Like radiosurgery approaches already used clinically, MRT is administered in one single treatment session or, possibly, in two or three fractions at most. Contrary to the homogeneous dose distribution at the target, clinical radiosurgery is administered as spatially variable total dose, doses being prescribed to well under the 100% isodose. Since not specifically stimulated tumours are non-synchronous with regard to cell cycle, tumours with a high proliferative index (number of proliferating cell per field of view, represented by the Ki-76 / MIB-1 index) should respond better than tumours with a lower proliferation index. Since the proliferation index is not specific for a tumour entity but varies individually between patients, rather than identifying a tumour entity best suited to MRT, the index should be assessed for each patient's tumour individually before a treatment recommendation is given.

However, tumour cell kill depends not only on direct hits but includes parameters with delayed action, staggered on a time scale.[16] Multiple events such as bystander and abscopal effects, changes on proteomic and genomic levels and vascular responses in tumour and normal tissue contribute to the final therapeutic efficacy. Thus, it remains to be proven how important a factor a high proliferation index is for therapeutic efficacy.

In patients with cancers of the musculoskeletal system such as sarcomas and chondrosarcomas, the prognosis is often determined by the development of metastatic disease. The quality of life during the remaining life span can be significantly increased by obviating the need for the amputation of an arm or leg when the primary tumour can be controlled. A new therapeutic approach which can control the primary tumour might not be able to prevent the development of metastatic disease, but could delay its development. Remarkable tumour responses have been seen after macroscopic grid therapy, even if the damage to normal tissue was significant.[104] Since it has been shown that normal tissue tolerance increases when the width of the beams is reduced to microscopic dimensions,[105] we expect significantly fewer adverse effects both morphologically and functionally after MRT, without markedly reducing tumour control.

MRT has shown to have considerable therapeutic potential in small animal models.[14,71] Irradiation with monoplanar beam arrays as well as in pencilbeam technique has caused only minimal functional deficits in the brain at peak doses significantly higher than those currently used in conventional radiotherapy.[60,69,103] It is hoped to see similar function-preserving effects when using MRT in the lung while maintaining an effective antitumour effect.

In clinical radiotherapy, the overall X-ray dose administered to lung tissue is limited due to the risk of debilitating lung fibrosis. The integration of an MRT boost in a conventional irradiation schedule might allow a reduction in the number of conventional radiotherapy fractions at equal dose and thus reduce the risk of fibrosis while high peak doses could contribute to an improved local tumour control. However, this remains still speculative and is not yet proven by experimental data.

To advance pre-clinical work towards clinical trials in a timely manner, all European and most overseas research groups working on different aspects of MRT have collaborated in a COST action supported by the European Union from 2013 to 2017. This has accelerated the development of MRT towards clinical trials at a speed otherwise impossible. In order to validate the results of the mathematical modeling for larger and more deep-seated tumours than those in small animal models and to correlate pathophysiologic and histological consequences in larger animals subjected to

MRT, two larger animal studies have been initiated in 2017. These studies will focus both on normal tissue tolerance to MRT and on therapeutic efficacy. It is hoped that the results of those experiments help in advancing the plans for a human clinical trial.

At the current stage of the technical development, a synchrotron with an integrated beamline/experimental facility dedicated to biomedical work is essential to generate the high flux primary X-ray beam required as a prerequisite for microbeams with dose rates above 100 Gy /s^{-1}. However, the development of compact X-ray sources is already underway by several companies and academic institutions internationally.[106–109] A successful Phase I clinical trial of MRT might be a sufficiently strong facilitator to push the development of compact sources to a point that would more readily allow a successful transfer of the technique into the clinical environment. This assumption had also been supported by the industrial side.[110]

CONCLUSION

Based on these results of pre-clinical work it appears reasonable to plan an MRT Phase I clinical trial to validate its feasibility and safety for patients. Two scenarios are expected to be in the focus of clinical interest: on the one hand, improved tumour control in patients with tumour entities which are seen as highly radioresistant with conventional radiotherapy approaches. On the other hand, MRT might hold a hope for the treatment of patients with otherwise therapy-refractive epilepsy.

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